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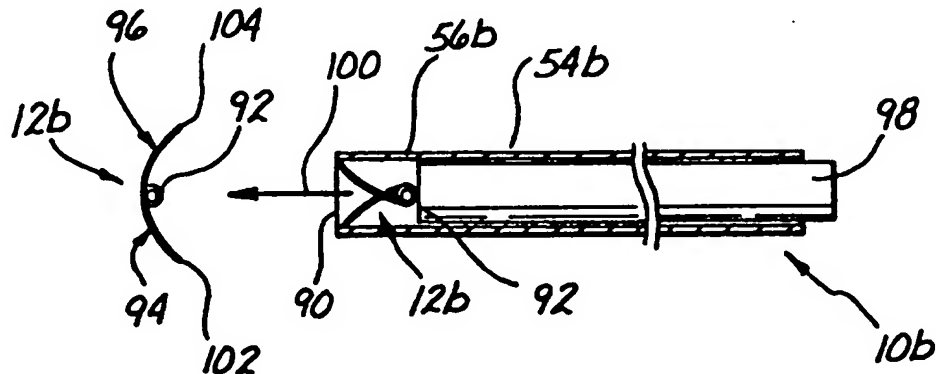
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(54) Title: METHODS AND DEVICES FOR DEFINING AND MARKING TISSUE

(57) Abstract

In order to later identify the location of a biopsy or surgery, various means and methods for permanently and non-surgically marking selected tissue in the human body are used. Later visualization of the markers is readily accomplished using state-of-the-art imaging systems.



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METHODS AND DEVICES FOR DEFINING AND MARKING TISSUE

Background of the Invention

This invention relates to methods and devices for marking and defining particular locations in human tissue, and more particularly relates to methods and devices for permanently defining the location and margins of lesions detected in a human breast.

5 It is desirable and often necessary to perform procedures for detecting, sampling, and testing lesions and other abnormalities in the tissue of humans and other animals, particularly in the diagnosis and treatment of patients with cancerous tumors, pre-malignant conditions and other diseases or disorders. Typically, in the case of cancer, when a physician establishes by means of known procedures (i.e. 10 palpation, x-ray, MRI, or ultrasound imaging) that suspicious circumstances exist, a biopsy is performed to determine whether the cells are cancerous. Biopsy may be an open or percutaneous technique. Open biopsy removes the entire mass (excisional biopsy) or a part of the mass (incisional biopsy). Percutaneous biopsy on the other hand is usually done with a needle-like instrument and may be either a fine needle 15 aspiration (FNA) or a core biopsy. In FNA biopsy, very small needles are used to obtain individual cells or clusters of cells for cytologic examination. The cells may be prepared such as in a Papanicolaou (Pap) smear. In core biopsy, as the term suggests, a core or fragment of tissue is obtained for histologic examination which may be done via a frozen section or paraffin section. The chief difference between 20 FNA and core biopsy is the size of the tissue sample taken. A real time or near real time imaging system having stereoscopic capabilities, such as the stereotactic guidance system described in U.S. Patent No. 5,240,011, is employed to guide the extraction instrument to the lesion. Advantageous methods and devices for performing core biopsies are described in the assignee's co-pending patent application

SN 08/217,246, filed on March 24, 1994, and herein incorporated by reference.

Depending upon the procedure being performed, it is sometimes desirable to completely remove suspicious lesions for evaluation, while in other instances it may be desirable to remove only a sample from the lesion. In the former case, a major
5 problem is the ability to define the margins of the lesions at all times during the extraction process. Visibility of the lesion by the imaging system may be hampered because of the distortion created by the extraction process itself as well as associated bleeding in the surrounding tissues. Although the lesion is removed and all fluids are continuously aspirated from the extraction site, it is likely that the process will
10 "cloud" the lesion, thus impairing exact recognition of its margins. This makes it difficult to ensure that the entire lesion will be removed.

Often, the lesion is merely a calcification derived from dead abnormal tissue, which may be cancerous or pre-cancerous, and it is desirable to remove only a sample of the lesion, rather than the entire lesion, to evaluate it. This is because such a
15 lesion actually serves to mark or define the location of adjacent abnormal tissue, so the physician does not wish to remove the entire lesion and thereby lose a critical means for later re-locating the affected tissue. One of the benefits to the patient from core biopsy is that the mass of the tissue taken is small. However, oftentimes, either inadvertently or because the lesion is too small, the entire lesion is removed for
20 evaluation, even though it is desired to remove only a portion. Then, if subsequent analysis indicates the tissue to be malignant (malignant tissue requires removal, days or weeks later, of tissue around the immediate site of the original biopsy), it is difficult for the physician to determine the precise location of the lesion, in order to perform necessary additional procedures on adjacent potentially cancerous tissue.
25 Additionally, even if the lesion is found to be benign, there will be no evidence of its location during future examinations, to mark the location of the previously removed calcification so that the affected tissue may be carefully monitored for future reoccurrences.

Thus, it would be of considerable benefit to be able to permanently mark the location or margins of such a lesion prior to or immediately after removing or sampling same. Marking prior to removal would help to ensure that the entire lesion is excised, if desired. Alternatively, if the lesion were inadvertently removed in its entirety, marking the biopsy site immediately after the procedure would enable re-establishment of its location for future identification.

A number of procedures and devices for marking and locating particular tissue locations are known in the prior art. For example, location wire guides, such as that described in U.S. Patent No. 5,221,269 to Miller et al, are well known for locating lesions, particularly in the breast. The device described by Miller comprises a tubular introducer needle and an attached wire guide, which has at its distal end a helical coil configuration for locking into position about the targeted lesion. The needle is introduced into the breast and guided to the lesion site by an imaging system of a known type, for example, x-ray, ultrasound, or magnetic resonance imaging (MRI), at which time the helical coil at the distal end is deployed about the lesion. Then, the needle may be removed from the wire guide, which remains in a locked position distally about the lesion for guiding a surgeon down the wire to the lesion site during subsequent surgery. While such a location system is effective, it is obviously intended and designed to be only temporary, and is removed once the surgery or other procedure has been completed.

Other devices are known for marking external regions of a patient's skin. For example, U.S. Patent No. 5,192,270 to Carswell, Jr. discloses a syringe which dispenses a colorant to give a visual indication on the surface of the skin of the point at which an injection has or will be given. Similarly, U.S. Patent No. 5,147,307 to Gluck discloses a device which has patterning elements for impressing a temporary mark in a patient's skin, for guiding the location of an injection or the like. It is also known to tape or otherwise adhere a small metallic marker, e.g. a 3 millimeter diameter lead sphere, on the skin of a human breast in order to delineate the location

of skin calcifications (see Homer et al, *The Geographic Cluster of Microcalcifications of the Breast*, Surgery, Gynecology, & Obstetrics, December 1985). Obviously, however, none of these approaches are useful for marking and delineating internal tissue abnormalities, such as lesions or tumors.

5 Still another approach for marking potential lesions and tumors of the breast is described in U.S. Patent No. 4,080,959. In the described procedure, the skin of the portion of the body to be evaluated, such as the breasts, is coated with a heat sensitive color-responsive chemical, after which that portion of the body is heated with penetrating radiation such as diathermy. Then, the coated body portion is
10 scanned for color changes which would indicate hot spots beneath the skin surface. These so-called hot spots may represent a tumor or lesion, which does not dissipate heat as rapidly because of its relatively poor blood circulation (about 1/20 of the blood flow through normal body tissue). This method, of course, functions as a temporary diagnostic tool, rather than a permanent means for delineating the location
15 of a tumor or lesion.

 A method of identifying and treating abnormal neoplastic tissue or pathogens within the body is described in U.S. Patent No. 4,649,151 to Dougherty et al. In this method, a tumor-selective photosensitizing drug is introduced into a patient's body, where it is cleared from normal tissue faster than it is cleared from abnormal tissue.
20 After the drug has cleared normal tissue but before it has cleared abnormal neoplastic tissue, the abnormal neoplastic tissue may be located by the luminescence of the drug within the abnormal tissue. The fluorescence may be observed with low intensity light, some of which is within the drug's absorbance spectrum, or higher intensity light, a portion of which is not in the drug's absorbance spectrum. Once detected,
25 the tissue may be destroyed by further application of higher intensity light having a frequency within the absorbance spectrum of the drug. Of course, this method also is only a temporary means for marking the abnormal tissue, since eventually the drug will clear from even the abnormal tissue. Additionally, once the abnormal tissue has

been destroyed during treatment, the marker is destroyed as well.

It is also known to employ biocompatible dyes or stains to mark breast lesions. First, a syringe containing the colorant is guided to a detected lesion, using an imaging system. Later, during the extraction procedure, the surgeon harvests a tissue sample from the stained tissue. However, while such staining techniques can be effective, it is difficult to precisely localize the stain. Also, the stains are difficult to detect fluoroscopically and may not always be permanent.

Additionally, it is known to implant markers directly into a patient's body using invasive surgical techniques. For example, during a coronary artery bypass graft (CABG), which of course constitutes open heart surgery, it is common practice to surgically apply one or more metallic rings to the aorta at the site of the graft. This enables a practitioner to later return to the site of the graft by identifying the rings, for evaluative purposes. It is also common practice to mark a surgical site with staples, vascular clips, and the like, for the purpose of future evaluation of the site.

A technique has been described for the study of pharyngeal swallowing in dogs, which involves permanently implanting steel marker beads in the submucosa of the pharynx (S.S. Kramer et al, *A Permanent Radiopaque Marker Technique for the Study of Pharyngeal Swallowing in Dogs, Dysphagia*, Vol. 1, pp. 163-167, 1987). The article posits that the radiographic study of these marker beads during swallowing, on many occasions over a substantial period of time, provides a better understanding of the pharyngeal phase of deglutition in humans. In the described technique, the beads were deposited using a metal needle cannula having an internal diameter slightly smaller than the beads to be implanted. When suction was applied to the cannula, the bead sat firmly on the tip. Once the ball-tipped cannula was inserted through tissue, the suction was broken, thereby releasing the bead, and the cannula withdrawn.

Of course, this technique was not adapted or intended to mark specific tissue sites, but rather to mark an entire region or structure of the body in order to evaluate

anatomical movements (i.e. swallowing motions). It also was not intended for use in humans.

Accordingly, what is needed is a method and device for non-surgically implanting potentially permanent markers at the situs of a lesion or other abnormal tissue, for the purpose of defining the margins of a lesion before it is removed and/or to establish its location after it has been removed. The markers should be easy to deploy and easily detected using state of the art imaging techniques.

Summary of the Invention

This invention solves the problems noted above by providing an implantable device which is particularly adapted to mark the location of a biopsy or surgery for the purpose of identification. The device is remotely delivered, preferably percutaneously. Visualization of the marker is readily accomplished using various state of the art imaging systems. Using the invention, it is possible to permanently mark the location or margins of a lesion or other tissue site, prior to removing or sampling same. The markers function to provide evidence of the location of the lesion after the procedure is completed, for reference during future examinations or procedures.

More particularly, a device is provided for marking tissue within a human body to identify a selected location for a diagnostic or therapeutic procedure. The device comprises a marker element and an apparatus for remotely delivering the marker element from outside the human body to the selected tissue location. Since, with remote delivery (e.g. percutaneously) direct visual access is not possible, an aided visualization device is used, such as an imaging system, an endoscope, or the like. Deployment of the marker element is such that it becomes implanted in the tissue.

The delivery apparatus preferably includes a member, which may comprise a

tube, such as a needle, cannula, or trocar, of any known type for delivering medications, surgical equipment, or other items to the interior of a patient's body. The member may also be the body of an optical instrument such as an endoscope, laparoscope, or arthroscope. In the preferred embodiment, a biopsy needle or gun, such as is often used to extract tissue for examination in a biopsy procedure, is used in conjunction with the marking device, comprising a portion of the delivery apparatus, in order to provide a means for entering the patient's body and positioning the marker element at the selected tissue location. However, in other embodiments, the marking device is self contained, having a means itself for obtaining entry to the body, and being guided by a commercially available guidance system, such as a stereotactic guidance system.

The aforementioned member or tube, which typically comprises a cannula or needle having a lumen, has a distal end portion or region and a proximal end portion or region, and is adapted to extend through the body. The distal region is adapted to retain and deploy the marker element and the proximal region is linked to the distal region, so that predetermined marker deployment functions may be communicated from the proximal region to the distal region. In some embodiments, these deployment functions are communicated by means of the marker elements themselves travelling through the lumen for deployment from the distal region. In other embodiments, an actuator extends axially through the lumen to communicate deployment functions to the marker element held on or by the distal region. The apparatus is preferably guided to the selected tissue location, i.e. the site of the detected lesion or other abnormality, using a stereotactic guidance system or similar imaging system.

Several alternative embodiments of the marking device are disclosed. In one embodiment, the distal region of the tube includes a forming die, which is adapted to form each marker element into a predetermined shape, preferably a helix, as the marker element is deployed from the lumen. In a number of alternative embodiments,

a mechanism, such as a mandrel, is used to push the marker elements through the tube. The marker elements may comprise a pre-formed spring having a predetermined shape, which is compressed into a linear position within the tube lumen. Upon deployment from the lumen, the spring is adapted to expand and
5 assume its predetermined shape to such an extent that the energy of its expansion is sufficient to implant the marker element into the tissue at the selected tissue location. In some embodiments, implantation is accomplished because the marker elements have a plurality of attachment elements, each having a tip end (sometimes sharpened) which expands outwardly with sufficient energy to embed and anchor itself into the
10 tissue at the selected tissue location. In other embodiments, the marker element has blunt, rather than sharpened edges, but is adapted to expand sufficiently upon exiting from the tube that its edges press radially against the selected tissue, thereby wedging and implanting the marker element.

In yet another embodiment of the invention, the tube lumen is adapted to
15 receive a deployment actuator connector, or center wire, which extends axially through the lumen. The connector includes a distal portion which extends distally of the tube and a proximal portion which extends proximally of the tube. The proximal portion is attached to a deployment actuator, such as a pull ring, while the distal portion is attached to the marker element. On the connector, proximal to the distal
20 portion, is a predetermined failure point which is adapted to be the weak point on the connector by failing first under tension. In operation, once the tube distal region has been positioned at the selected tissue location, the deployment actuator is actuated in a proximal direction to pull the marker element against the distal region of the tube. The tube distal region thus functions as a forming die to cause the marker element to
25 bend until it abuts the tube distal region at its junction with the distal portion of the connector, such that the marker element is reconfigured to a desired shape. The proximal portion of the connector is adapted to be severed from the distal portion at the predetermined failure point upon the application of continued tension on the

deployment actuator after abutment of the marker element against the tube distal region, thereby releasing and implanting the marker element.

Another important feature of the invention is the ability to utilize marker elements having a plurality of shapes. In some embodiments, these shapes may be created merely by utilizing different sized material stock or different cross sections. This shape diversity permits the adoption of a system wherein each shape denotes a different selected tissue location or event.

In a preferred embodiment of the invention, the device is adapted to be employed in combination with a medical instrument which transports the device to the selected tissue location responsive to positional control by a guidance system. The medical instrument preferably draws a vacuum to isolate and retain tissue at the selected location in a tissue receiving port. The marking device is adapted to deploy the marker element into the retained tissue.

In another aspect of the invention, a marker element is provided for marking tissue within a human body to identify a selected location for a diagnostic or therapeutic procedure. The marker element, which is preferably comprised of a biocompatible, implantable, and substantially radiopaque material, is adapted to be deployed to the selected tissue location percutaneously by a delivery instrument, so as to become implanted in the tissue.

A number of different marker element configurations and materials may be employed. Materials may include stainless steel, titanium, and the like, as well as non-metallic materials, such as polymers, salts, and ceramics, for example. In some embodiments, the marker element may actually be formed into a desired shape by a forming die in the delivery instrument, while in other embodiments, it may comprise a spring which radially expands upon exit from the delivery instrument to embed itself in the tissue.

In yet another aspect of the invention, a method for permanently marking tissue in a human body to identify a selected location for a diagnostic or therapeutic

procedure is disclosed, which comprises actuating a delivery instrument, having a tube with a distal region, to a position wherein the tube extends through the human body and the distal region is at the selected location. A marker element is then deployed from the tube distal region to the selected tissue location so that it becomes anchored in the tissue.

These and other aspects and advantages of the present invention are set forth in the following detailed description and claims, particularly when considered in conjunction with the accompanying drawings in which like parts bear like reference numerals.

10

Brief Description of the Drawing

Fig. 1 is a cross-sectional view of a biopsy instrument embodiment as described in co-pending patent application SN 08/217,246, configured to be utilized as a preferred instrument for use in conjunction with the inventive tissue marking device;

15 Figs. 2 and 3 are cross-sectional views illustrating the sequential steps in the operation of the biopsy instrument embodiment needed to capture tissue targeted for marking;

Fig. 4 is a cross-sectional view of one embodiment of a tissue marking device constructed in accordance with the principles of the invention, illustrating the device in a first position in preparation for delivering a marker to tissue targeted for marking;

20

Fig. 4A is an enlarged cross-sectional view of the region of Fig. 4 denoted by lines 4A, illustrating the marker in greater detail;

Fig. 5 is a cross-sectional view similar to Fig. 4, illustrating a first sequential step for delivering the marker to the targeted tissue;

Fig. 5A is an enlarged cross-sectional view of the region of Fig. 5 denoted by lines 5A, illustrating the marker in greater detail;

Fig. 6 is a cross-sectional view similar to Figs. 4 and 5, illustrating a second sequential step for delivering the marker to the targeted tissue;

5 Fig. 6A is an enlarged cross-sectional view of the region of Fig. 6 denoted by lines 6A, illustrating the marker in greater detail;

Fig. 7 is a cross-sectional view similar to Figs. 4-6, illustrating a third sequential step for delivering the marker to the targeted tissue;

10 Fig. 7A is an enlarged cross-sectional view of the region of Fig. 7 denoted by lines 7A, illustrating the marker in greater detail;

Fig. 8 is a cross-sectional view similar to Figs. 4-7, illustrating a fourth sequential step for delivering the marker to the targeted tissue;

Fig. 8A is an enlarged cross-sectional view of the region of Fig. 8 denoted by lines 8A, illustrating the marker in greater detail;

15 Figs. 9, 10, and 11 are schematic cross-sectional views of an alternative embodiment of a tissue marking device constructed in accordance with the principles of the invention, illustrating sequentially the delivery of a marker to the targeted tissue;

20 Fig. 12 is a schematic cross-sectional view illustrating a third alternative embodiment of a tissue marking device constructed in accordance with the principles of the invention;

Fig. 13 is a schematic cross-sectional view illustrating a fourth alternative embodiment of a tissue marking device constructed in accordance with the principles of the invention;

5 Fig. 14 is a schematic cross-sectional view illustrating a fifth alternative embodiment of a tissue marking device constructed in accordance with the principles of the invention;

Fig. 15 is a schematic cross-sectional view illustrating a sixth alternative embodiment of a tissue marking device constructed in accordance with the principles of the invention;

10 Fig. 16 is a schematic cross-sectional view illustrating a seventh alternative embodiment of a tissue marking device constructed in accordance with the principles of the invention;

Fig. 17 is a front elevation view of an alternative marker element embodiment;

15 Fig. 18 is a perspective view of another alternative marker element embodiment;

Fig. 19 is a front elevation view of yet another alternative marker element embodiment; and

Fig. 20 is a front elevation view of still another alternative marker element embodiment.

Detailed Description of the Invention

Now with more particular reference to the drawings, Figs. 4, 4A, 5, 5A, 6, 6A, 7, 7A, 8, and 8A illustrate sequentially the deposit of a marker into a desired tissue location, utilizing a preferred embodiment of the invention. Specifically, the marking instrument 10 comprises a marker element 12 which includes an umbrella end comprising a pair of attachment members or wings 14 and 16, and a center wire 18. All three wires 14, 16 and 18 are joined at the distal end 20 of the center wire 18, preferably by welding. At the proximal end 22 of the center wire is a deployment actuator or pull ring 24, which is preferably attached by welding or brazing.

To place the marker element 12 at a desired location, a biopsy needle or gun is preferably used, though other known delivery means could be used as well. For example, the stand-mounted biopsy instrument described in U. S. Patent Application SN 08/217,246, previously incorporated by reference into this application, is a preferred instrument for introducing the marker element into the body of a patient. One embodiment of such an instrument 26 is partially illustrated in Figs. 1-3. The biopsy instrument 26 includes a housing 28. A hollow outer piercing needle 38 is attached to the housing 28 at location 34. A distal end of the hollow outer piercing needle 38 includes a point 40. Hollow outer piercing needle 38 also includes a tissue receiving port or bowl 42 (Figs. 2 and 3). A cannular inner cutter 44 is movably positioned coaxially within the hollow outer piercing needle 38 and housing 28. A vacuum line 46 supplies vacuum to ports 50 in the bottom of the receiving bowl 42.

Operation of the biopsy instrument to facilitate the placement of a tissue marker is illustrated sequentially in Figs. 1-3. Fig. 1 illustrates the distal end point 40 of the hollow outer piercing needle 38 in position to pierce a target tissue 51. The initial position of the point 40 with respect to the tissue area being marked is determined by the overall position of the biopsy instrument with respect to the patient.

A detailed description of such a motorized biopsy needle positioner, i.e. stereotactic guidance system, is given in U.S. Patent No. 5,240,011, issued on August 31, 1993 to Michael Assa, which is hereby incorporated herein by reference. The suspect lesion within tissue 51 is to be targeted and marked according to the instructions provided with the stereotactic guidance system. As shown in Fig. 1, the stereotactic guidance system has positioned the biopsy instrument 26 such that the distal end point 40 is immediately adjacent to the surface of the tissue 51. Once the point 40 is adjacent the specific lesion to be marked, the needle 38 is fired into the lesion such that the point 40 traverses through the lesion, thereby placing the tissue receiving bowl 42 in the center of the lesion.

As shown in Fig. 2, after the hollow outer piercing needle 38 has been positioned at the precise location within the tissue 51 at which it is desired to mark tissue, the cutter 44 is moved proximally of the housing 28 to provide an entry access for the tissue marker delivery system.

As shown in Fig. 3, a vacuum source attached to vacuum line 46 is actuated, thereby generating a region of low pressure at the vacuum ports 50 to facilitate the prolapse of tissue 51a immediately adjacent to the tissue receiving port 42 into the hollow interior of hollow outer piercing needle 38.

Now again referring to Figs. 4, 4A, 5, 5A, 6, 6A, 7, 7A, 8, and 8A, the marking instrument 10 includes a tube 54. The center wire 18 runs axially through a lumen 56 of the tube 54, with the pull ring 24 being attached to the proximal end of the center wire 18, proximally of the tube 54. The distal end 20 of the center wire extends distally of the tube 54 and is joined to attachment members 14 and 16, as described above.

In operation, the tube 54 of the marking instrument is inserted into the patient's body in the direction of the arrow 58, as shown in Fig. 4, until the distal end 20 of the center wire 18 approaches the desired location, adjacent to or in the abnormal tissue or lesion. Because direct visual access to the targeted tissue is

impossible, an aided visualization device, such as the stereotactic guidance system described above, is used to guide the distal portion of the marking instrument to the targeted tissue. Then, if the biopsy instrument shown in Figs. 1-3 is utilized to deploy the markers, the targeted tissue 51a (Fig. 5) is vacuumed into the tissue receiving port
5 42. Referring particularly to Figs. 5 and 5A, once the distal end 20 of the center wire reaches the targeted, vacuumed tissue, the ring 24 is pulled away from the tissue in the direction of the arrow 60. This action deploys the marker attachment members 14 and 16 as they are forced into a die formed in the tip 62 of the tube. This die may take any desired form, depending upon the desired deployed configuration of the
10 attachment members 14, 16.

With reference to Figs. 6 and 6A, tension continues to be applied to the ring 24, in the direction shown by the arrow 64, until the distal end of the marker is fully deployed. Forcing the attachment members into the die 62 causes them to extend outwardly, as illustrated, into the tissue. Their outward energy anchors the marker
15 element 12 in the tissue for permanent implantation. The tips 66 and 68 of the attachment members may be configured to be less traumatic as an implant, or may alternatively be sharpened to provide a more secure grip. At full deployment, the width of the umbrella end of the marker element is preferably about .035 to .045 inches, though other sizes may be utilized within the scope of the invention.

Now referring to Figs. 7 and 7A, even after the attachment members 14 and 16 have been fully deployed, the pull ring 24 is pulled to further increase tension in the direction of the arrow 70, until the center wire 18 is sheared at a point of weakness or detent 72 (see Figs. 4A-6A) which is established in the center wire 18 proximally of the tip 20. Once failure has occurred, the pull ring 24 and the proximal
20 portion 18' of the center wire may be discarded as they are severed from the marker
25 element 12 and remaining distal portion 18" of the center wire.

Finally, with reference to Figs. 8 and 8A, to finish placing the marker element 12, the tube 54 is withdrawn in the direction of the arrow 74, as illustrated. The

marker element is thereby permanently secured to locate the lesion site for future examination by known imaging methods.

In the preferred embodiment, the marker element 12 is fabricated of stainless steel. However, many other biocompatible, radiopaque, implantable materials may be used for the marker element 12 as well, including, for example, titanium, tantalum, or nickel-titanium alloys. Additionally, while a 3-pronged umbrella end is shown and described, any number of prongs may be used, if desired.

While it is preferred that the marker element 12 be deployed using the biopsy instrument described and shown in Figs. 1-3, any instrument capable of delivering the element percutaneously may be utilized. Such instruments, for example, may include the hand-held biopsy gun described in U.S. Patent No. Re. 34,056, entitled "TISSUE SAMPLING DEVICE" and issued to Lindgren et al. All of these types of instruments include a tube (typically a cannula or needle) which is adapted to enter the body, and would be capable of delivering the marker element. It is also within the scope of the invention to deliver the marker element through any tube which has access to the body or using optical medical instruments, such as endoscopes, arthroscopes, or laparoscopes, in which case the marker element is delivered to the desired tissue site from outside the body of the patient, through the body of the instrument.

Now with reference to Figs. 9-11, an alternative embodiment of a marking instrument 10a is shown, which is identical to the instrument 10 in all respects not shown or described herein. Portions of the instrument 10a corresponding to portions of the instrument 10 are designated by corresponding reference numerals followed by the letter a.

The Fig. 9 embodiment is substantially similar to the Fig. 4 embodiment, in that the marking instrument includes a tube 54a which has a lumen 56a, and may utilize a cannula, needle, or imaging instrument (i.e. endoscope, laparoscope, or the like) for access to a delivery site within the body and to aid in delivery. Again, as is

the case for all succeeding embodiments, it is preferred that the tube 54a utilize the hollow outer piercing needle 38 of the biopsy instrument shown in Figs. 1-8, though any other instrument which is capable of delivering a marker percutaneously or through a body orifice from a location outside the patient's body may be utilized. A center wire 18a runs longitudinally through the lumen 56a. At the proximal end of the center wire 18a is a deployment actuator or pull ring 24a. At the distal end of the center wire is the marker element 12a.

A primary difference between the Fig. 4 and Fig. 9 embodiments is that the Fig. 9 marker element 12a is preferably a generally "U" shaped element resembling a surgical ligating clip, having tips 66a and 68a, which is captured by the distal looped end 20a of the twisted center wire. In operation, once the tips 66a and 68a of the marking element 12a reach the targeted tissue, the ring 24a is pulled rightwardly in the direction of the arrow 76 (Fig. 10). This action retracts the base portion 78 of the marker element 12a into a forming recess 80 (Fig. 9), wherein the recessed tube wall 82 forces prongs 86 and 88 together until tips 66a and 68a of the prongs 86 and 88, respectively, contact or nearly contact one another (Fig. 10). At this point, increasing tension applied to the pull ring 24a causes the wire 18a to fail at a point of weakness or detent (not shown) provided in the center wire at or near its tip end 20a, thereby releasing the marker into the target tissue, as illustrated in Fig. 11.

Referring now to Fig. 12, a second alternative embodiment of a marking instrument 10b is shown, which is identical to the instrument 10 in all respects not shown or described herein. Portions of the instrument 10b corresponding to portions of the instrument 10 are designated by corresponding reference numerals followed by the letter b.

The Fig. 12 embodiment is substantially similar to the Fig. 4 embodiment, in that the marking instrument includes a tube 54b which has a lumen 56b, and may utilize a cannula, needle, or imaging instrument (i.e. endoscope, laparoscope, or the like) for access to delivery site within the body and to aid in delivery.

There are two primary differences between the embodiments of Figs. 4 & 9 and that of Fig. 12. First, in the Fig. 12 embodiment, a plurality of marker elements 12b (two are shown, though any number may be employed) may be preloaded into the tube 54b, each comprising a pre-formed spring which is deployed through the tube's distal region 90 in an axial direction. Second, the nature of the deployment mechanism utilizes a compressive rather than tensile force. It may further be noted that, though end deployment of the marker elements in the Fig. 12 embodiment is illustrated, they may be similarly deployed radially through a side port (not shown) in tube 54b, or at any other angle, to accommodate delivery through an existing instrument (i.e. cannula, needle, endoscope, laparoscope, or the like). In being deployed radially, the distal region 90 is not used for passage of the marker element and could be utilized to house a piercing element (not shown) similar to that shown in Figs. 1-3. Armed with the piercing element, this marker delivery system would not be dependent on a positioning system as described in Figs. 1-3 for placement at the tissue site and could be used alone in conjunction with a commercially available stereotactic or other guidance system. This concept may be applied to all subsequent embodiments except that illustrated in Fig. 16.

Still with reference to Fig. 12, each marker element or spring 12b preferably includes a center coil 92 from which a pair of attachment members 94 and 96 extend, and is adapted to automatically attach itself to the target tissue by utilizing its own stored energy. Thus, in operation, each spring 12b is held in a compressed position within the tube 54b. When it is desired to deploy the marker, a mandrel 98 is preferably utilized to push the spring 12b through the center lumen 56b and out through the distal open end 90 of the tube. Once the spring exits the tube, stored energy causes the attachment members 94 and 96 to expand outwardly, as shown. As this expansion occurs, the tips 102 and 104 of the attachment members 94 and 96, respectively, anchor themselves into the tissue to permanently secure the marker element in the desired location. As with the Fig. 4 embodiment, the tips 102 and

104 may be blunt to be less traumatic as an implant, or may alternatively be sharpened or barbed to provide a more secure grip. Once a spring has been deployed, the instrument may be repositioned to the next desired location for the immediate deployment of another marker until the supply in the tube 54b is exhausted,
5 eliminating the need to remove and re-load the marking instrument 10b between each deployment.

Again in this embodiment, the spring 12b may be fabricated of any known biocompatible, implantable, radiopaque material, though stainless steel is preferred. Additionally, the forces required to deploy the attachment members on the spring may
10 be customized by varying the spring filar, dimensions, material, and/or the number of coils in the torsional part of the spring.

Fig. 13 illustrates another alternative embodiment of the marking instrument 10. This is identical to the instrument 10b of Fig. 12 in all respects, not specifically described herein. Portions of the instrument 100c corresponding to portions
15 instrument 10b of Fig. 12 are designated by corresponding reference numerals followed by the letter c.

In actuality, the Fig. 13 embodiment is substantially identical to that of Fig. 12, except for the shape of each spring 12c, and is employed in precisely the same manner. Thus, to deploy a marker element 12c, the mandrel 98c is utilized to push
20 the spring 12c through the center lumen 56c and out through the distal open end 90c of the tube. As in the Fig. 12 embodiment, the marker element travels in the direction of the arrow 100c, until the attachment members 94c and 96c extend outwardly sufficiently to anchor themselves to the target tissue. Also, the Fig. 13 embodiment is similar to the Fig. 12 embodiment in that the instrument may be re-
25 positioned to immediately deploy another marker element without re-loading, and marker elements may be deployed radially through a side port in tube 54c (not shown), or any other angle, to accommodate delivery through an existing instrument (i.e. cannula, needle, endoscope, laparoscope, or the like).

Fig. 14 shows still another alternative embodiment of the marking instrument 10, which is also substantially identical to the instrument 10b of Fig. 12 in all respects not shown or described herein. Portions of the instrument 10d corresponding to portions of the instrument 10b of Fig. 12 are designated by corresponding reference numerals followed by the letter d.

Again, the Fig. 14 embodiment is substantially identical to those of Figs. 12 and 13, except for the shape of the marker element or spring 12d. A marker element 12d is deployed preferably using a mandrel 98d or the like to push the spring 12d through the center lumen 56d until it exits through the open end 90d of the tube. As in the Figs. 12 and 13 embodiments, the marker element travels in the direction of the arrow 100d, until the tips 102d and 104d extend outwardly sufficiently to anchor themselves to the target tissue.

In practice, a radiologist or other operator of the equipment can use a marker shaped like marker 12b, as shown in Fig. 12, during one biopsy, then use a differently shaped marker, such as the marker 12c in the Fig. 13 embodiment, or the marker 12d in the Fig. 14 embodiment, during a subsequent biopsy procedure. The differently shaped markers permit the distinction between different biopsy procedures during future imaging procedures, as well as between biopsy sites which may be close in proximity, thereby improving the information available to the radiologist and thus the ability to monitor or diagnose the patient's future condition more precisely.

Fig. 15 illustrates yet another alternative embodiment of the marking instrument 10, which is also substantially identical to the instrument 10b of Fig. 12 in all respects not shown or described herein. Portions of the instrument 10e corresponding to portions of the instrument 10b of Fig. 12 are designated by corresponding reference numerals followed by the letter e.

In this embodiment, each marker element 12e is deployed distally through the open distal region 90e of the tube 54e by a mandrel 98e, much as in the previous embodiments shown in Figs. 12, 13, and 14. The primary difference, however,

between this embodiment and the previous embodiments is that, while the marker elements in the previous embodiments rely largely on the barbed nature of the spring to secure themselves in the tissue, in this embodiment, the springs are secured simply because of their significant expansion upon exit from the tube. This embodiment particularly lends itself to marking the boundaries of a biopsy or other desired site by defining the perimeter of the site. The expansion of the spring 12e causes the blunt edges 102e and 104e to press outwardly against the selected tissue, thereby wedging the spring securely into position.

An advantage of this embodiment is that, because of the tight compression of the springs 12e within the tube 54e, a larger number of markers can be inserted therein simultaneously, thereby permitting the deployment of more markers without having to pause and disengage to re-load.

Another advantage the Fig. 15 embodiment provides is the ability to deploy springs adapted to expand to a number of different sizes all from the same lumen. Larger sized springs would require more coils within a given lumen than smaller sized springs (not shown).

It should be noted that the springs need not be limited to the configuration illustrated, but could include any spring of any configuration which expands to secure its position. While stainless steel is presently preferred, any other biocompatible, implantable, and radiopaque material could be used alternatively. Also as in the previous embodiments, marker elements may be similarly deployed radially through a side port in tube 54e (not shown), or any other angle, to accommodate delivery through an existing instrument (i.e. cannula, needle, endoscope, laparoscope, or the like).

Still another alternative embodiment of the marking instrument 10 is shown in Fig. 16. In this embodiment, the marking instrument 10f comprises a tube 54f. Wire segments 106 of any desired length are preloaded into the lumen 56f, which runs along substantially the entire length of the tube 54f. Once the needle is properly

positioned, the marker elements 12f are deployed by pushing them out of the tip of the needle, through the side exit port 108. A curved portion 110 of the lumen 56f comprises a die portion, and is adapted to form the wire segments 106 into helical marker elements 12f as they pass therethrough, pushed by a mandrel (not shown) or other known means from the tip of the needle through the exit port 108. The nature of the curve or curves in the die portion 110 and preformed curves imparted into the wire segments determine the final shape (which resembles a partial or whole helix) and dimensions of the marker element.

This embodiment is versatile in that it is capable of continuously deploying any number of marker elements without the necessity of re-loading, since all that is required is a continuous feed of wire segments into the proximal region of the tube 54f. Furthermore, differently sized and shaped helixes may be delivered in the same procedure by utilizing marker wires of different diameters and/or preformed curves, which approximate different helical shapes as they pass through the die portion. Thus, loading a plurality of different sized wires into the needle yields a plurality of different shaped markers.

Of course, as with the previous embodiments, although stainless steel is presently preferred, many different types of biocompatible, implantable, and radiopaque materials could be utilized within the scope of the invention. Also as in the previous embodiments, marker elements may be similarly deployed at different angles to accommodate delivery through an existing instrument (i.e. cannula, needle, endoscope, laparoscope, or the like).

Unlike previous embodiments, Fig. 16 preferably incorporates a piercing element 112 enabling this marker to be delivered without the aid of the positioning system described in Figs. 1-3 for placement at the tissue site. This embodiment could be used alone in conjunction with a commercially available stereotactic or other (i.e. ultrasonic) guidance system.

Though a number of different embodiments of the conceptual invention have

been described and shown, it is considered to be within the scope of the invention for the marking elements and delivery instruments to take on many other forms.

For example, embolization coils like that illustrated in Fig. 17 and designated with reference numeral 12g are well known in the medical field for placement into vessels

5 such as veins and arteries in order to block off fluid flow abnormalities (such as fistulas and arteriovenous malformations). These coils have been made of various materials, including stainless steel, platinum, and gold, and are wound into configuration similar to that of a light bulb filament. They are generally placed into the body using a catheter or trocar system. The inventors in the present application
10 have discovered that such coils may indeed also be used as marker elements, for permanent implantation in target tissue, in a manner similar to that described previously with respect to Figs. 1-16.

Marker elements of many other materials and configurations may be used as well. For example, one such multi-appendaged jack-shaped marker 12h is illustrated
15 in Fig. 18. Additionally, small beads 12i (Fig. 19) of calcium carbonate or other radiodense materials, which are highly visible by mammographic imaging, could be deployed as marker elements. One such application would be to place a plurality of such beads or pellets (each having a diameter of about 500 μ) around the entirety of a breast lesion prior to the extraction procedure, which would then serve as guides to
20 ensure that all of the margins had been removed. During subsequent imaging procedures, they would function to denote the location of the previous biopsy for reference purposes.

Referring now to Fig. 20, yet another alternative marker element 12j, which is of a woven construction, is illustrated. Other such marker materials may include
25 adhesives and epoxies which would be injected at the biopsy site. Biodegradable polymers and other plastics could also be used, as long as they are biocompatible, implantable, and visible using an imaging system.

While this invention has been described with respect to various specific

examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A device for marking tissue within a human body to identify a selected location for a diagnostic or therapeutic procedure, comprising:
a marker element; and
an apparatus for remotely delivering said marker element from outside the
5 human body to the selected tissue location, using an aided visualization device;
wherein said marker element becomes implanted in said selected tissue location.
2. A device as recited in claim 1, wherein said apparatus includes a member having a distal region and a proximal region, said member being adapted to extend through said human body, wherein said distal region is adapted to retain and deploy said marker element and said proximal region is linked to said distal region, so
5 that predetermined marker deployment functions may be communicated from said proximal region to said distal region.
3. A device as recited in claim 2, wherein said apparatus comprises a distal region which is adapted to pierce said human body.
4. A device as recited in claim 2, wherein said marker element may travel along said member from said proximal region to said distal region for deployment therefrom.
5. A device as recited in claim 2, wherein said distal region includes a forming die, which is adapted to form said marker element into a predetermined shape as the marker element is deployed from said member.

6. A device as recited in claim 5, wherein said predetermined shape is substantially helical.

7. A device as recited in claim 4, wherein said member comprises a tube having a lumen extending axially therethrough, the proximal region of the tube being adapted to receive said marker element so that it may travel axially through said lumen to the distal region of the tube.

8. A device as recited in claim 7, wherein said apparatus is adapted to draw a vacuum through said tube.

9. A device as recited in claim 7, wherein said apparatus further comprises a mandrel which is adapted to push said marker element through said tube lumen.

10. A device as recited in claim 7, wherein said marker element comprises a pre-formed spring having a predetermined shape which is compressed into said tube lumen, and is adapted to expand upon deployment from said distal region, such that the expansion of the spring implants the marker element into the tissue at said
5 selected tissue location.

11. A device as recited in claim 10, wherein said marker element further comprises a plurality of attachment members, said attachment members each being adapted to expand when the marker element is released from said tube lumen, such that each attachment member expands with sufficient energy to embed itself into the
5 tissue at the selected tissue location, thereby implanting the marker element.

12. A device as recited in claim 10, wherein said marker element is

deployed within tissue at said selected tissue location, the marker element being adapted to expand sufficiently that the edges thereof press against said tissue to implant the marker element.

13. A device as recited in claim 2, wherein said member is adapted to receive a deployment actuator connector which extends axially therealong, said connector comprising a distal portion which extends distally of the member and a proximal portion which extends proximally of the member, said proximal portion
5 being attached to a deployment actuator and said distal portion being attached to said marker element, wherein actuation of said deployment actuator is transmitted from the proximal portion of the connector to the distal portion thereof to cause release and deployment of said marker element.

14. A device as recited in claim 13, and further comprising a predetermined failure point in the distal region of said deployment actuator connector, wherein once the distal region of said member is positioned at said selected tissue location, the deployment actuator may be actuated to pull the marker element against
5 the distal region of said member, said member distal region being adapted to function as a forming die to cause the marker element to bend until it encounters a stop designed into said member distal region, such that the marker element is reconfigured to a desired shape, the proximal portion of said connecting means being adapted to be severed from the distal portion at said predetermined failure point upon the further
10 actuation of said deployment actuator after abutment of the marker element against said stop, thereby releasing and implanting said marker element.

15. A device as recited in claim 1, and further comprising a plurality of marker elements adapted to assume a plurality of shapes, wherein each shape denotes a different selected tissue location or event.

16. A device as recited in claim 1, wherein said device is adapted to be employed in combination with a medical instrument which transports said device to said selected tissue location responsive to positional control by a guidance system.

17. A device as recited in claim 16, wherein said medical instrument draws a vacuum to isolate and retain tissue at the selected location and said marking device is adapted to deploy said marker element into said retained tissue.

18. A device as recited in claim 7, wherein said tube lumen is adapted to receive a plurality of marker elements.

19. A marker element for marking tissue within a human body to identify a selected location for a diagnostic or therapeutic procedure, said marker element being comprised of a biocompatible and implantable material and being deployable to the selected tissue location percutaneously by a delivery apparatus, such that the marker
5 element becomes implanted in said tissue.

20. A marker element as recited in claim 19, wherein said marker element is formed into a predetermined shape upon exiting said delivery apparatus and becoming implanted in said tissue.

21. A marker element as recited in claim 19, wherein said marker element includes sharp edges or protrusions adapted to pierce tissue and thereby become anchored therein.

22. A marker element as recited in claim 19, wherein said marker element comprises a radiopaque material.

23. A marker element as recited in claim 22, wherein said material is metallic.

24. A marker element as recited in claim 22, wherein said material is non-metallic.

25. A marker element as recited in claim 19, wherein said marker element comprises a plurality of attachment members, each of which has a tip end adapted for implantation into said tissue.

26. A marker element as recited in claim 25, wherein said plurality of attachment members are spring loaded such that they expand, the expansion functioning to implant said plurality of attachment members into said tissue.

27. A marker element as recited in claim 19, wherein said marker element comprises a spring which is adapted to expand upon deployment from said delivery apparatus, the expansion functioning to implant the marker element into said tissue.

28. A marker element as recited in claim 19, wherein said tissue location is a lesion in a human breast.

29. A method for permanently marking tissue in a human body to identify a selected location for a diagnostic or therapeutic procedure, the method comprising:

- a) manipulating a delivery apparatus having a distal region to a position wherein the apparatus extends through the human body and the distal region is at the selected location, and
- b) deploying a marker element into said selected tissue location, such that it becomes substantially permanently implanted in the tissue.

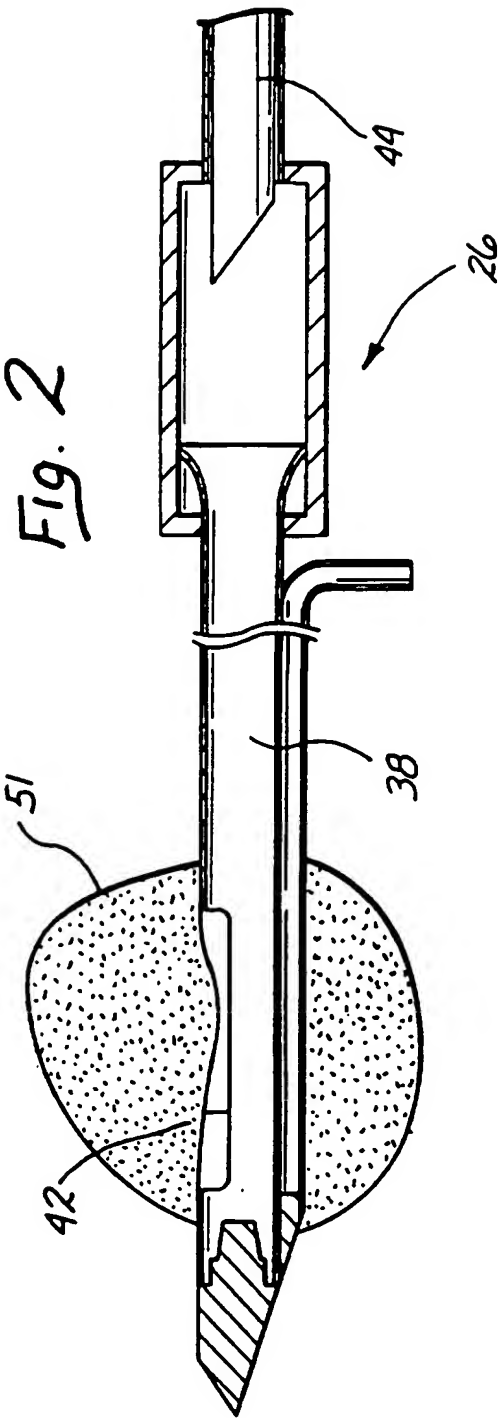
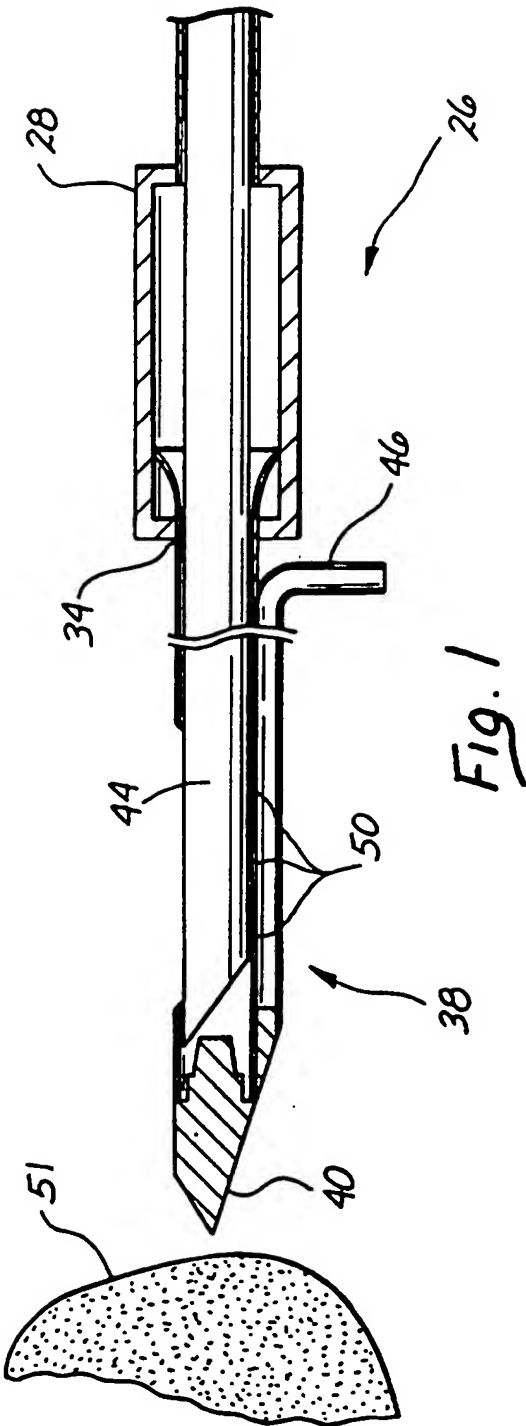
30. The method as recited in claim 29, wherein said deployment step includes the step of forming and releasing said marker element.

31. The method as recited in claim 29, wherein said deployment step includes the release of said marker element from the distal region of said delivery apparatus.

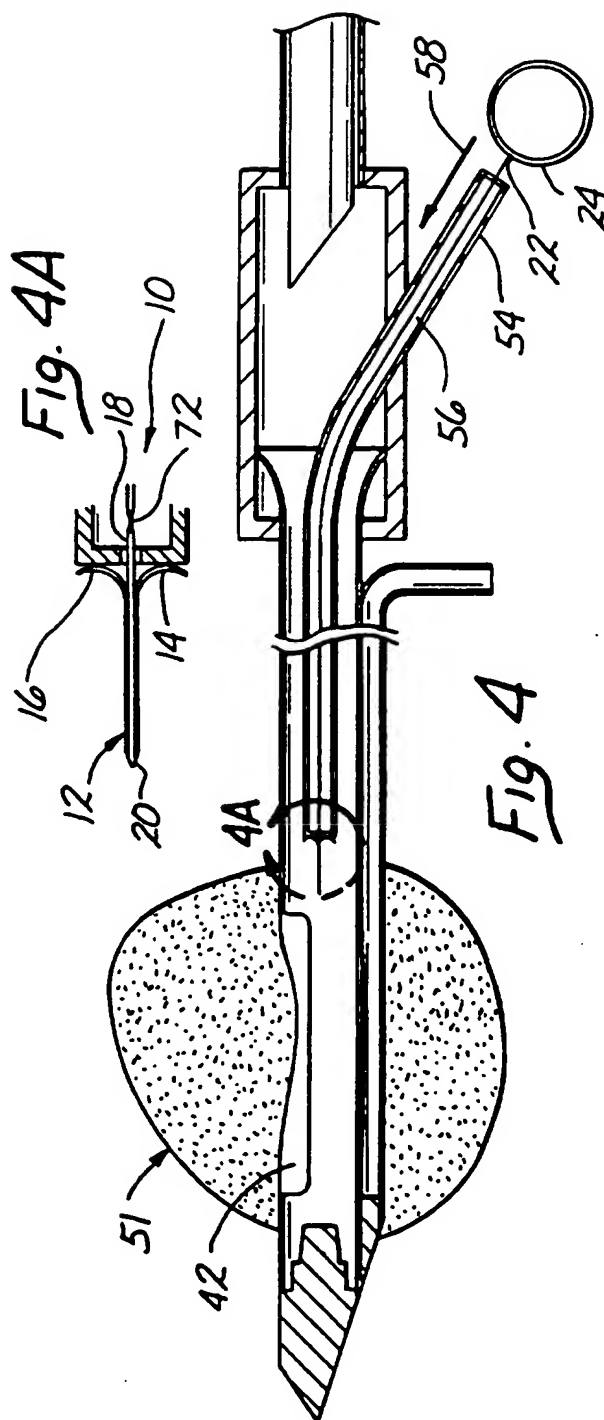
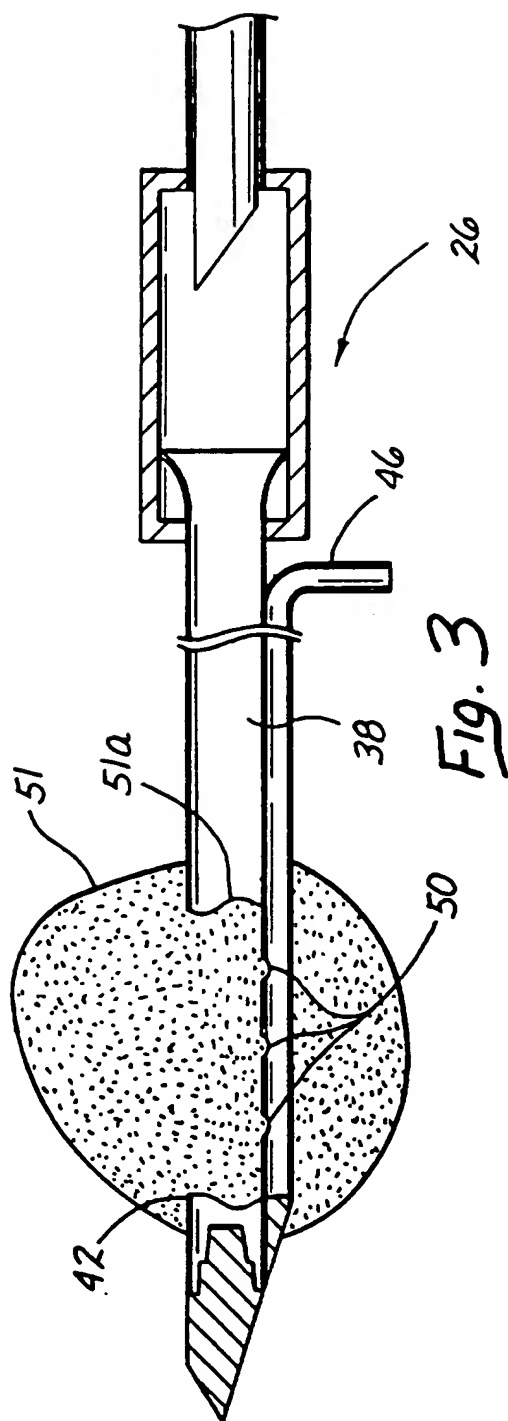
32. The method as recited in claim 29, wherein said deployment step includes the step of drawing tissue from said selected tissue location into a tissue receiving port in said delivery apparatus, and deploying said marker element into the tissue in said tissue receiving port.

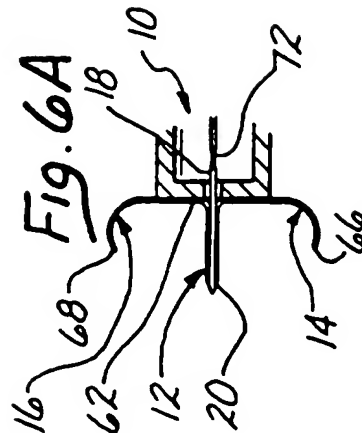
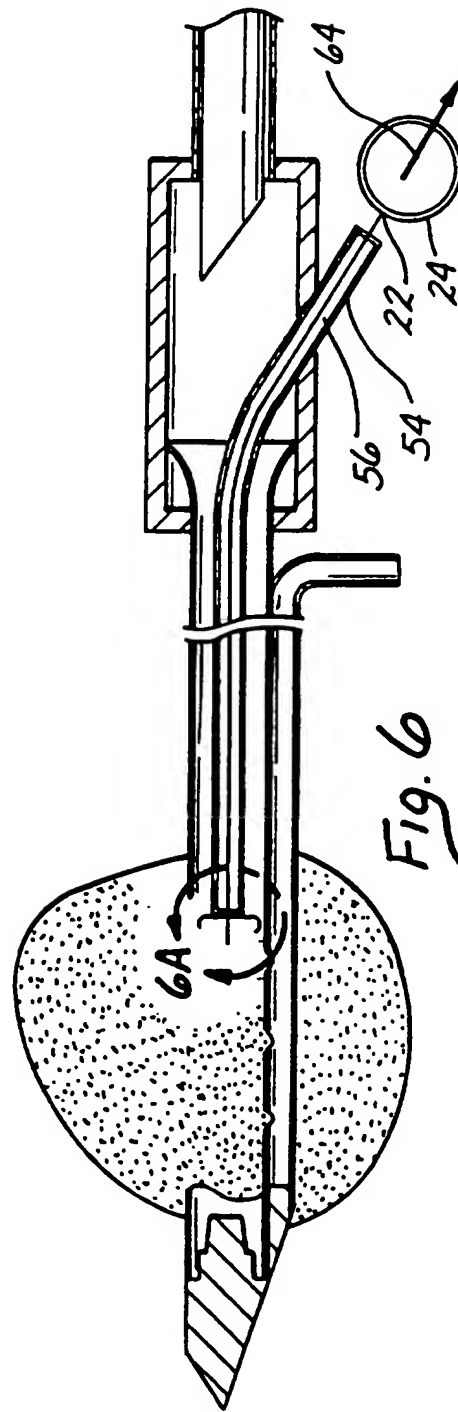
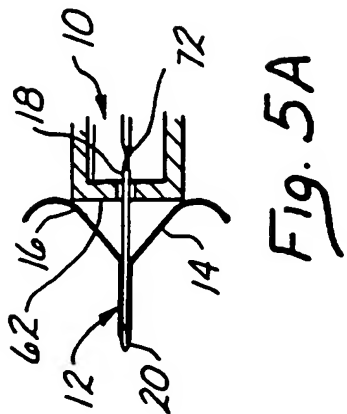
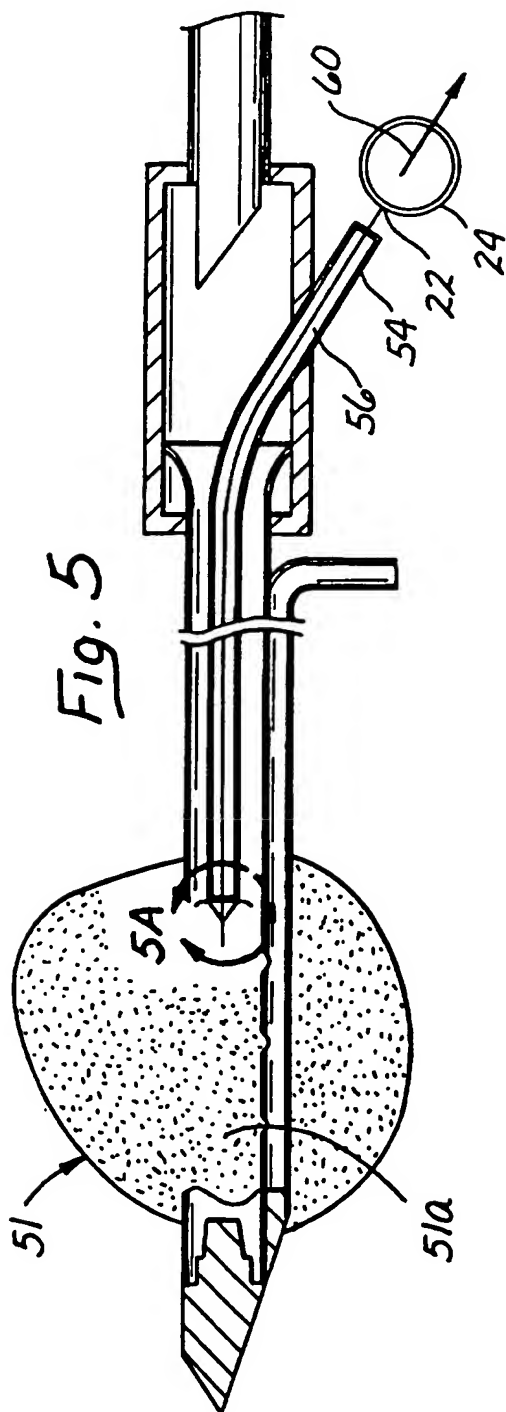
33. The method as recited in claim 29, wherein said deployment step includes the step of actuating a deployment actuator to form and release said marker element.

34. The method as recited in claim 29, wherein said deployment step includes the step of actuating a mechanism to release said marker element from said distal region.

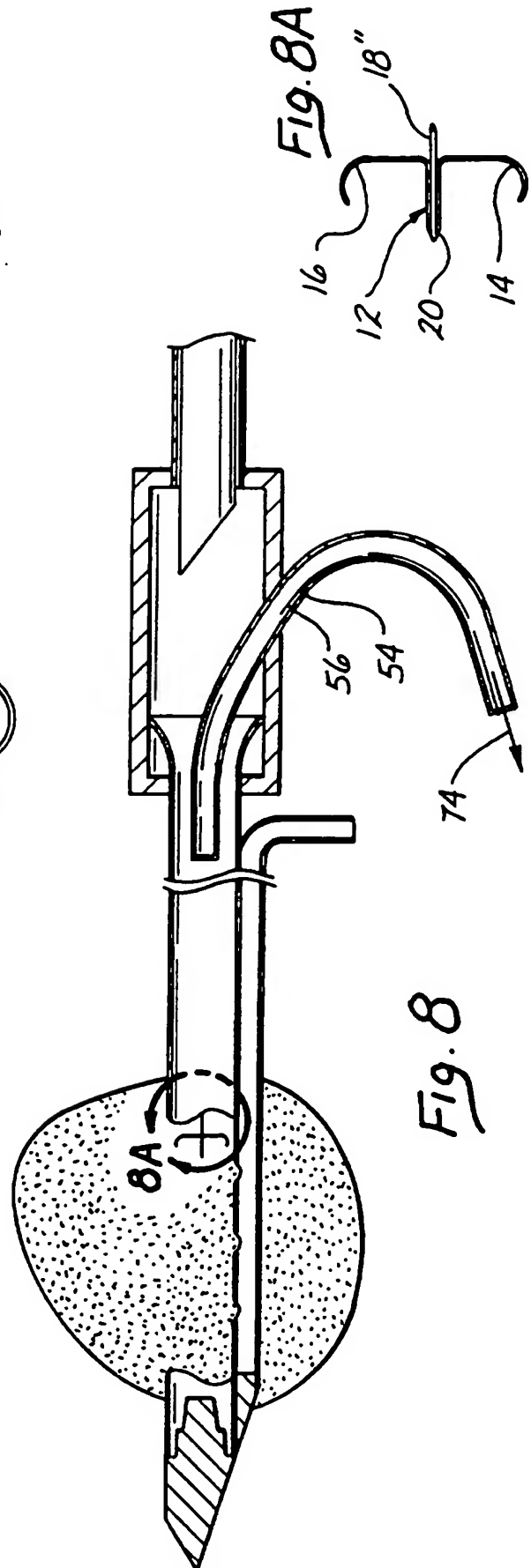
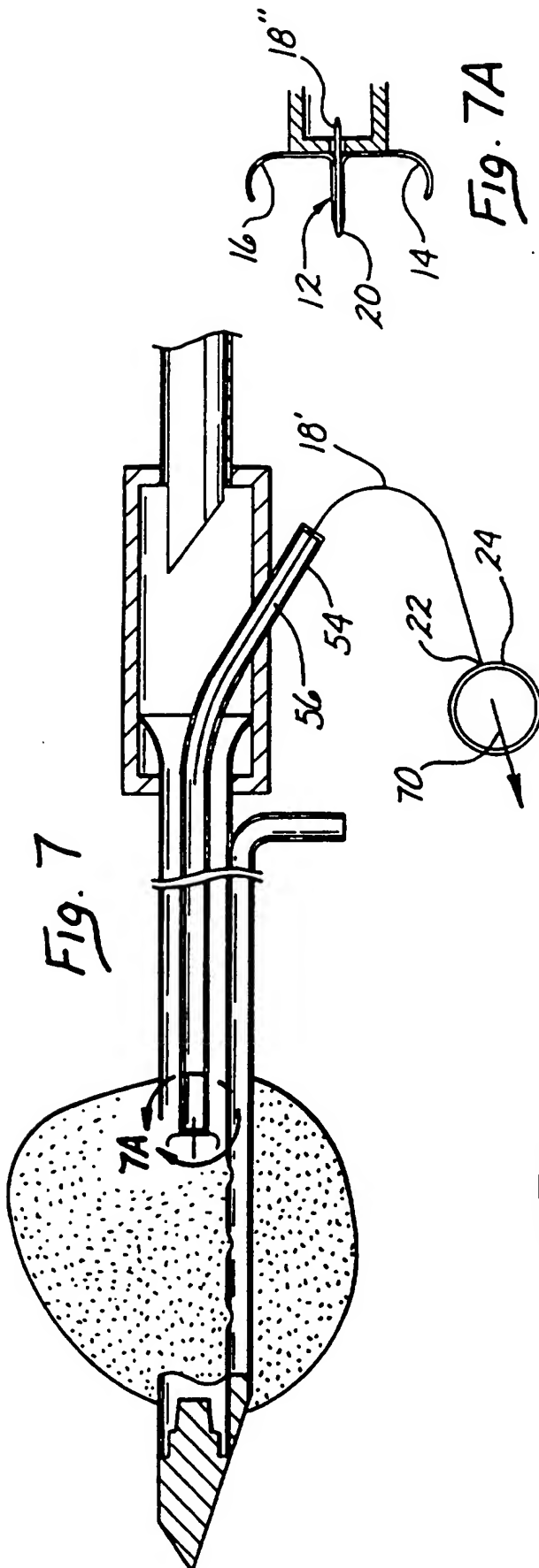


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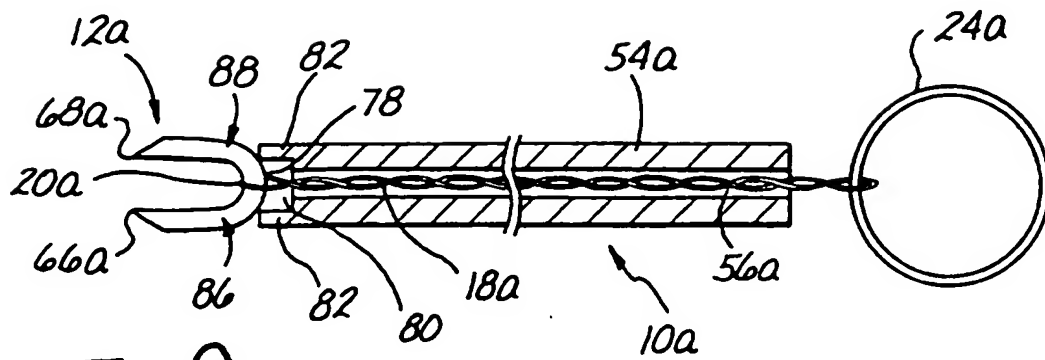


Fig. 9

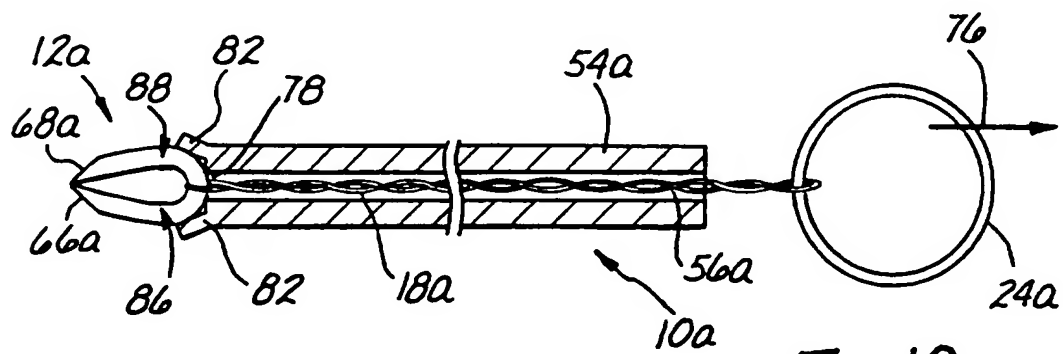


Fig. 10

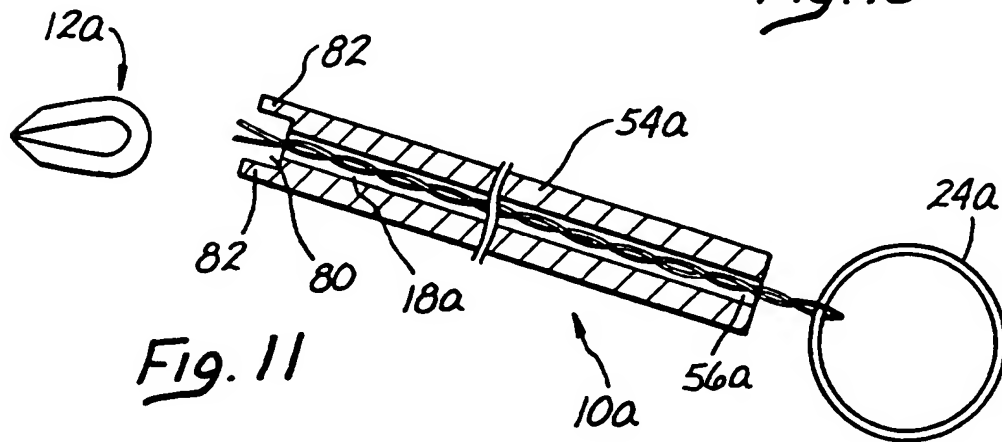


Fig. 11

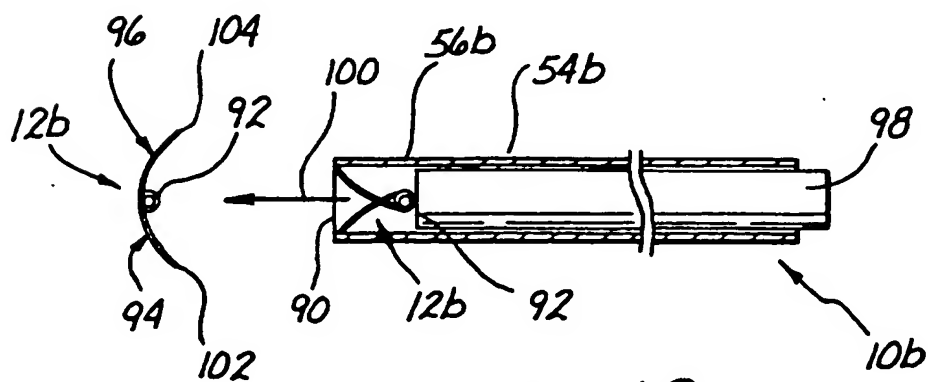
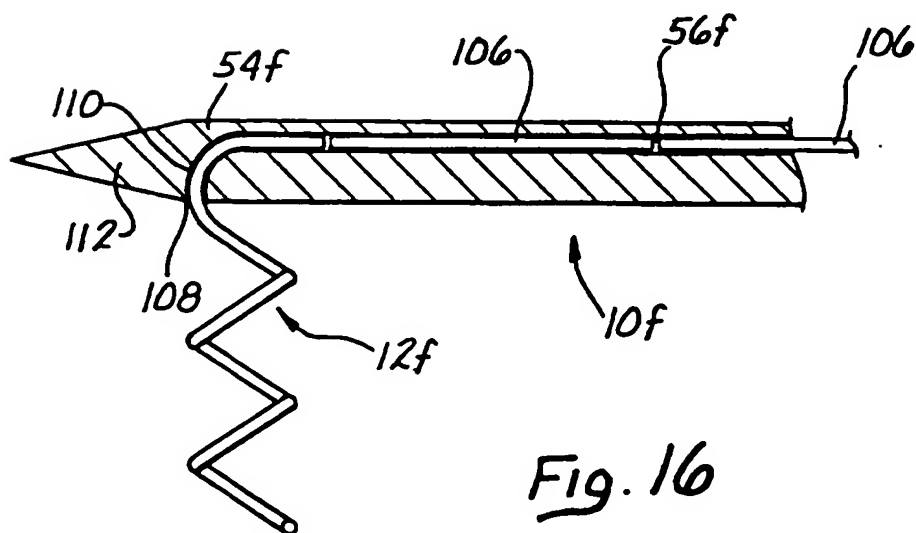
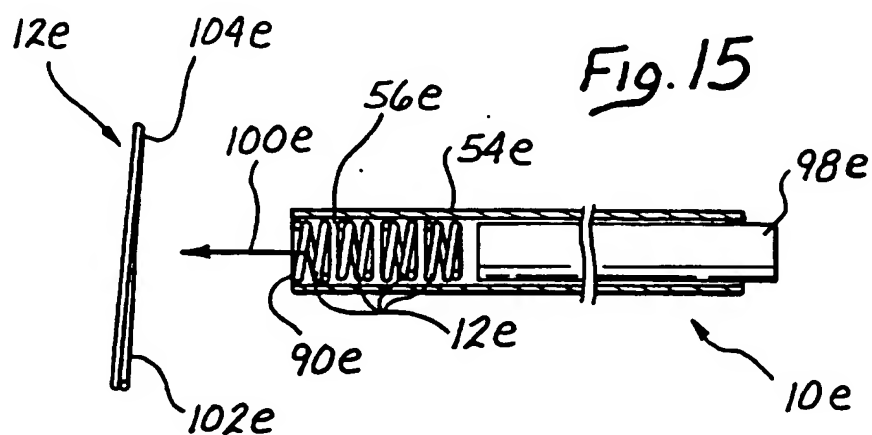
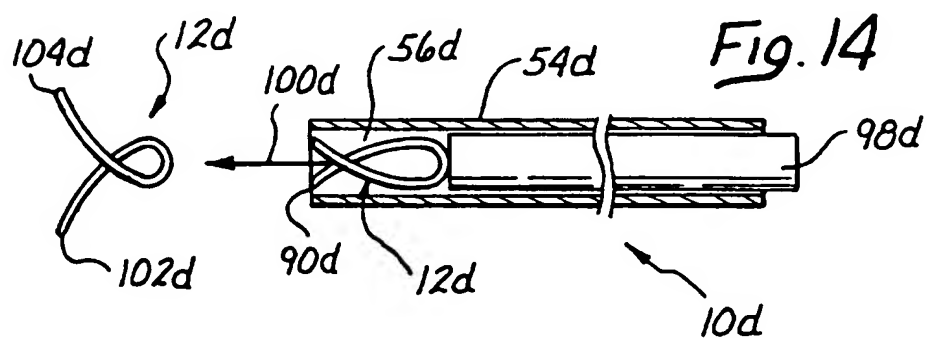
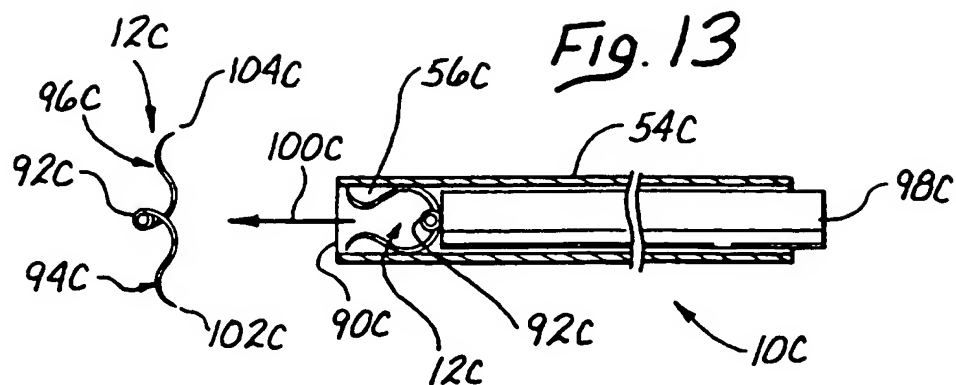
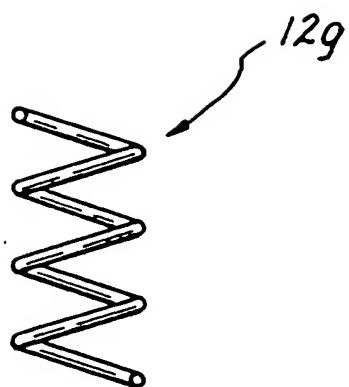
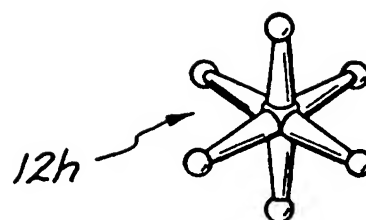
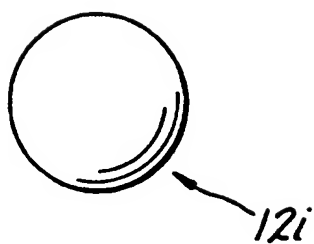
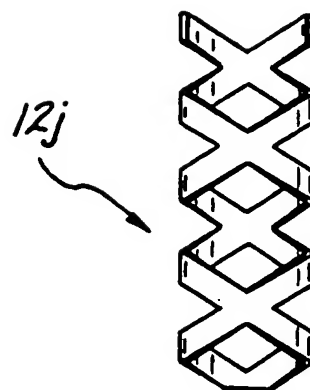


Fig. 12

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*Fig. 17**Fig. 18**Fig. 19**Fig. 20*

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 95/11558

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61B19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61B A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 146 699 (SULZER) 3 July 1985	1,2,13, 15,16, 19,20, 22,23
Y	see page 3, last paragraph - page 4, paragraph 3; figures 1,2	3,4,7,8, 10,17, 21,24, 27,28
X	--- EP,A,0 293 605 (MEDITECH) 7 December 1988 see column 5, last paragraph see column 8, last paragraph - column 9, paragraph 1; figures 3,10 --- -/--	1,2,4, 7-12

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

17 January 1996

Date of mailing of the international search report

26. 01. 96

Name and mailing address of the ISA

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Authorized officer

Barton, S

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 95/11558

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 350 043 (PALESTRANT) 10 January 1990 see column 10, paragraph 3; figures 4-6 ---	1,2,4,7, 10-13, 19-23, 25-27
X	US,A,4 693 237 (HOFFMAN) 15 September 1987 see claims 1-4 ---	1,15,19, 22,23
X	US,A,4 682 606 (DECAPRIO) 28 July 1987 see abstract; figures 3,16 ---	1,19
Y	EP,A,0 481 685 (COOK) 22 April 1992 see abstract; figures 5,7 ---	3,4,7,8, 10,17, 21,27,28 5,6,20
Y	GB,A,2 132 091 (BARD) 4 July 1984 see page 1, line 112 - line 117 ---	24
A	US,A,4 909 250 (SMITH) 20 March 1990 see abstract; figures 1,3,4,6 ---	9
A	WO,A,93 19803 (BOSTON SCIENTIFIC) 14 October 1993 see abstract; figure 5; example 3 ---	1,11
A	WO,A,90 15576 (RESEARCH CORPORATION TECHNOLOGIES) 27 December 1990 see page 17, line 16 - line 17; figures 6,7 ---	1,19
A	US,A,5 195 540 (SHIBER) 23 March 1993 see abstract; figures 1,6 -----	1,19

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/11558

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 29-34
because they relate to subject matter not required to be searched by this Authority, namely:
PCT Rule 39.1 (iv)
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 95/11558

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-146699	03-07-85	CH-A- 661199	15-07-87
EP-A-293605	07-12-88	US-A- 4817600 CA-A- 1287782 DE-A- 3883078 DE-T- 3883078 ES-T- 2042635 JP-A- 1052476	04-04-89 20-08-91 16-09-93 03-03-94 16-12-93 28-02-89
EP-A-350043	10-01-90	US-A- 4832055 CA-A- 1315634	23-05-89 06-04-93
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